

# Brain-stem lesions after head injury

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A full description of brain-stem injuries should include their mechanisms and types of damage, distinguishing those which are primary and occur at the time of the injury, from those which are secondary and result from changes elsewhere in the brain or in other parts of the body; and the various lesions should be related to the clinical condition of the patients. Unfortunately, knowledge is insufficient to allow any of these objectives to be satisfactorily fulfilled. Morphological studies on human material are necessarily limited to fatal cases, and largely to examples of severe injury. Knowledge of brain-stem changes after relatively minor head injuries is fragmentary. It depends on the occasional case recovering or recovered from a non-fatal head injury and dying of some other cause coming into the hands of a pathologist sufficiently interested to study the brain-stem in detail. This paper consists primarily of an account of the morphological changes in the brain-stem in injured patients; mechanisms are not discussed and reference to other factors concerned is made only when this is essential.

Many accounts of brain-stem injury have been restricted to descriptions of the haemorrhages which occur in rapidly fatal cases, and the lesions, often haemorrhagic, which result from increase of supratentorial mass. Important as these are, it cannot be too strongly emphasized that lesions of different kinds and origins occur in the brain-stem after injury. The full spectrum of change can be appreciated only when cases surviving different periods of time are extensively examined using a variety of staining procedures. Severe lesions may be present though the brain-stem appears normal or nearly so to the naked eye.

Primary haemorrhages are first described and then the secondary lesions from tentorial herniation which tend to differ in distribution and are often partly or largely ischaemic. Other less well

recognized changes and their distribution are then described. Often they are the result of primary injury but are recognizable by present histological techniques only in those who survive hours or days. Finally, the changes which occur in the brain-stem of patients surviving in coma for long periods are briefly stated and related to the other findings.

## Primary Brain-stem Haemorrhages

Haemorrhages are usually the only evidence of injury to the brain-stem in those dying immediately or within a few hours. They may be visible to the naked eye or only microscopically. Failure to realize this has led to underestimates of the frequency of brain-stem haemorrhage after injury, and indeed to the frequency of brain-stem lesions of all kinds. Thus, Jellinger (1967) reported that only 43.5% of 415 fatal head injuries showed evidence of brain-stem lesions, but extensive histology was done only in the 38 cases dying after prolonged coma. Tandon and Kristiansen (1966) report a group of 37 fatal cases with brain-stem symptomatology in whom no structural damage was seen at necropsy, but histological studies were not apparently done. In cases with brain-stem symptomatology, Zoltan (1966) found no lesions at that level and was prepared to seek the origin of the symptoms in cortical and sub-cortical damage. By contrast, Matsuoka, Sakaki, and Okamoto (1967) in a careful histological study found haemorrhagic lesions in the brain-stem in 22 out of 25 cases, and Mayer (1967) found them in all his 25 cases dying within an hour of injury. Mayer plotted primary brain-stem haemorrhages only from such a group.

Primary haemorrhages are usually small and

tend to have a special distribution. First, they are often present in the subependymal tissues around the third and fourth ventricles and in the periaqueductal grey matter; extension of bleeding into the ventricles is frequent. Second, they often affect the lateral structures of the brain-stem, and though any part may be damaged, the tissues near the lateral mesencephalic sulcus, the superior cerebellar peduncles, the colliculi, and the basis pedunculi are probably most frequently involved. In addition, the midline ventral structures of the rostral brain-stem and hypothalamus may be affected. Microscopy is frequently needed to detect many of the haemorrhages. Figure 1 shows diagrammatically the distribution of haemorrhages in a case dying within minutes of injury and in which only the larger rostral lesions were visible to the naked eye.

Microscopically the bleeding may be periarterial, perivenous, or pericapillary or it may disrupt the tissues without any apparent relation to a vessel in a single section. To assume that the type of vessel giving rise to the bleeding can be deduced from the site of the extravasated blood as Matsuoka *et al* (1967) have done would seem unwise, but Mayer (1967) stated that the laterally situated haemorrhages are predominantly arterial and those near the ventricles are mostly venous. In multiple sections he identified torn arteries in 17 and torn veins in 21 of his 25 cases. In a few cases capillaries were apparently torn from arterioles.

In the writer's experience, haemorrhages into the rostral brain-stem are usually more numerous and severe than those in the medulla in rapidly fatal injuries. Indeed, the lower stem may escape completely and the most caudal haemorrhages may be situated at the junction of the mid-brain and diencephalon. However, laceration or severe contusion of the medulla or pons may be found in those with severe bone damage in the vicinity of the foramen magnum, such as fracture dislocations of the atlanto-occipital joint or fractures which run into the foramen. Primary haemorrhages, though widely distributed, are usually small in those who die quickly which suggests that they suffer an injury incompatible with life for more than a brief interval. As a corollary, and perhaps more important, this finding suggests that patients who are alive even a few hours after a head injury have not suffered widespread primary brain-stem haemorrhage, even of microscopic type. Further evidence for this is that even minute haemorrhages are only occasionally found in the medulla in those who survive more than a few hours, though small haemorrhages with distribution characteristic of primary bleeding, may be found rostral to the mid-pons even in cases surviving several days. The presence in a rapidly fatal case of several microscopic haemorrhages in multiple sections supports the notion that a brain-stem injury had occurred which had been incompatible with life for more than a

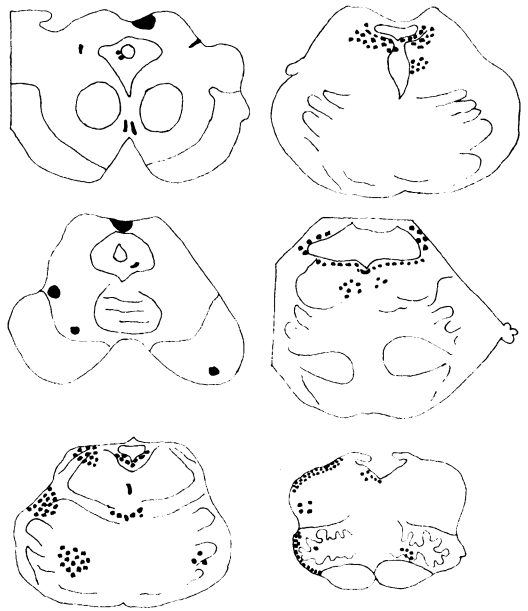


Fig. 1 Diagrammatic representation of the distribution of primary haemorrhages in the brain-stem from a girl of 15 years who died within 15 minutes of a road accident. A fracture in the occipital bone reached the left side of the foramen magnum. All the haemorrhages in the four caudal sections were microscopic.

brief period. It is not suggested that such haemorrhages are responsible for death; they merely indicate damage of a type and distribution which is incompatible with life.

### Secondary Brain-stem Lesions following Tentorial Herniation

The secondary destructive lesions in the brain-stem are not confined to head injuries but may follow any increase of supratentorial mass. Their importance in head injuries is that they may produce a fatal issue in patients without brain-stem damage at the time of the injury. For example, patients who are not unconscious after injury or with only a short period of coma followed by a lucid interval, may develop subdural or extradural haemorrhage; then tentorial herniation and death from brain-stem lesions may occur, both potentially preventable by early surgery.

Great variation in brain-stem movement and distortion and consequent pathological change occurs with supratentorial space-occupying lesions. In cases of head injury, these are usually extra- or intracerebral haemorrhage, brain swelling, or a combination of these. In uncomplicated subdural or extradural bleeding the size of the

haematoma is obviously of great moment, though the volume of skull unoccupied by brain is also important. Thus, the cerebral atrophy of old age often allows a considerable amount of extracerebral haemorrhage to occur without severe effects on the brain-stem (Aronson and Okasaki, 1963). The speed of development of the supratentorial mass is also of significance, an observation experimentally confirmed by Weinstein, Langfitt, Bruno, Zaren, and Jackson (1968). Herniation may occur within a very short time of injury and then it may be very difficult or impossible to decide which of the resulting brain-stem haemorrhages are primary or secondary. The situation of the supratentorial mass and its unilateral or bilateral distribution largely determine whether or not significant lateral displacement of the stem will occur, but Sunderland (1958) and Corsellis (1958) have stressed the importance in variations in size and shape of the tentorial opening on the results of herniation. Sunderland (1958) detailed and beautifully illustrated the varying anatomical relations at tentorial level and discussed how these could affect the results of raised intracranial mass. All these considerations determine whether movement of the rostral brain-stem is mainly lateral or downwards or a combination of these with side-to-side compression. The importance of herniation of the medial temporal lobe has probably been overstressed; its occurrence depends *inter alia* on space being available at the tentorial opening.

Downward displacement produces marked elongation, distortion, and stretching of the mid-brain and often of the thalamus and hypothalamus. Howell (1961) has stressed that fixation of the medulla and upper cervical spinal cord greatly limits their possible downward displacement so that the upper brain-stem shortens and angulates backwards and literally buckles under sufficient pressure. Sunderland (1958) also stressed posterior displacement and rotation of the mid-brain and Weinstein *et al* (1968) showed that its dorsal surface was often displaced more caudally than the ventral surface.

Brain-stem herniation is therefore a complicated phenomenon. It is hardly surprising that the lesions found in fatal cases vary considerably, that different features are emphasized by different authors, or that disagreement still exists about the origins of lesions.

Some of the above features will not be appreciated at a routine necropsy when the brain is removed from above after cutting the tentorium at its attachments. Even then elongation and downward movement of the cerebral peduncles is often visible since the peduncles are more prominent than usual on the ventral surface, protruding abnormally from the hemispheres. Some lateral shift may also be seen. Marked downward displacement of the diencephalon with some lateral movement or twisting is often appre-

ciated, particularly on examining the mammillary bodies. Haemorrhages or necrosis in the hypothalamus or into the herniated medial temporal lobes or the occipito-temporal lobe are often visible in the uncut brain. The pons is often swollen. Transverse sections often confirm the downward displacement and elongation of the mid-brain and caudal diencephalon. Lateral shift is revealed by the eccentric position of the aqueduct which is almost invariably greatly narrowed and slit-like or totally closed. The side-to-side compression of the mid-brain and the anterior-posterior elongation with greater downward displacement of the dorsal in relation to the ventral structures is often easily appreciated. Distortion and downward movement are detectable usually only in the mid-brain and diencephalon though antero-posterior elongation may be visible in the upper pons.

The major effects of these movements and compressions are often visible macroscopically as small or gross haemorrhages, haemorrhages associated with infarction, or as infarction alone. Sometimes microscopy is needed to detect early infarcts which may be the only evidence of distortion of the stem. Haemorrhages are the most common obvious abnormality. The principal haemorrhages are usually midline in the upper pons and throughout the pontine and mid-brain tegmentum (Figs. 2 and 3) though they often

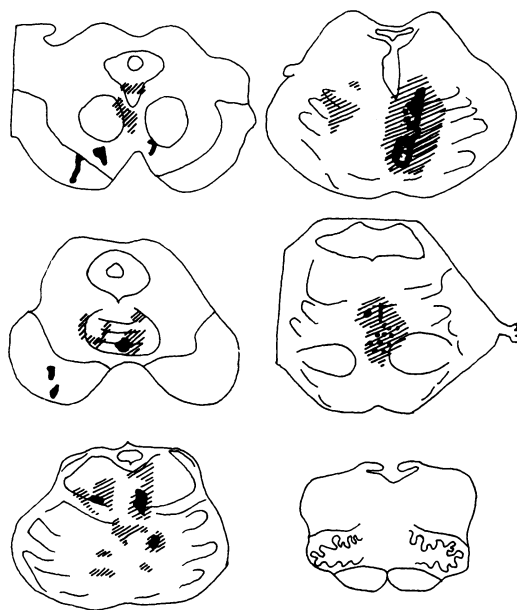


Fig. 2 Diagrammatic representation of secondary haemorrhage and infarction in the brain-stem from a man of 58 years who developed bilateral subdural haematomata without any history of trauma. The solid black areas represent haemorrhage, and the lines ischaemic necrosis.

spread almost to the lateral limits of the mid-brain. They may appear as numerous, small focal haemorrhages, but are often massive and confluent, spreading from the central rostral pons throughout the tegmentum to produce a butterfly-shaped haemorrhage. Sometimes they predominate on the lateral aspect of one cerebral peduncle on the side opposite to the supratentorial mass when the latter is predominantly unilateral; these result from pressure against the free edge of the tentorium. Extensive haemorrhage may extend into or rostral to the superior colliculi, involving the medial parts of each red nucleus and substantia nigra, and even disrupt the posterior thalamus and structures in the floor of the posterior third ventricle. When haemorrhage is gross, evidence of infarction may be minimal in surrounding tissues, but when haemorrhages are less massive, although extending over the same territory, they are almost invariably accompanied by surrounding macro- or microscopic infarction. Occasionally, infarction without haemorrhage occurs. The haemorrhages are mostly pericapillary or interstitial when they are small or not extensive, though perivenous haemorrhage around dilated veins may also be seen. In those surviving a few days, many axon retraction balls are often present in the vicinity of the haemorrhages or infarcts; in the occasional case with long survival, softenings with or without iron-laden macrophages will be found in the same areas (*vide infra*).

The frequency and severity of central lesions in the pons and tegmentum following herniation and the relative sparing of lateral mid-brain structures can be readily confirmed in most cases due to trauma or non-traumatic causes. Massive haemorrhage is probably a terminal event and may disrupt the entire rostral stem. In less severe cases and in those showing predominant infarc-

tion, central and paracentral structures are usually heavily involved (Wolman, 1953). Tomlinson (1964) illustrates the extensive mid-line destruction which may be found in those surviving in coma for long periods after herniation, and Strich (1969) shows a similar case of long survival in 'coma vigil' with smaller, widespread, but still predominantly central and paracentral lesions. Laterally placed pontine or mid-brain necrosis or haemorrhage due to herniation is rare in the absence of central lesions, though peripheral haemorrhages certainly occur in the contralateral cerebral peduncle due to lateral displacement by herniation, and other lateral lesions also may be seen.

Disagreement still exists about the origin of the mid-brain lesions in tentorial herniation. Any explanation must account for the frequent infarction, sometimes with little or no haemorrhage, and for the fact that some patients in deep coma for a short time from tentorial herniation recover completely on removal of the supratentorial clot. This evidence denies the place of haemorrhages from venous obstruction as the primary cause in many cases, though the presence of dilated veins and perivenous haemorrhage has produced advocates for the venous origin of the bleeding (Scheinker, 1945; Poppen, Kendrick, and Hicks, 1952; Stroobandt, Brucher, and van de Voorde, 1967). Infarction without haemorrhage indicates an arterial origin. There is much to support this view (Blackwood, 1963), including the evidence of torn small arteries obtained by injection studies (Johnson and Yates, 1956) and of considerable arterial distortion (Hassler, 1967). The coma in those recovering completely must have been due primarily to distortion of the stem and its functional disturbance without the irreversible ischaemia or haemorrhage which may occur subsequently.

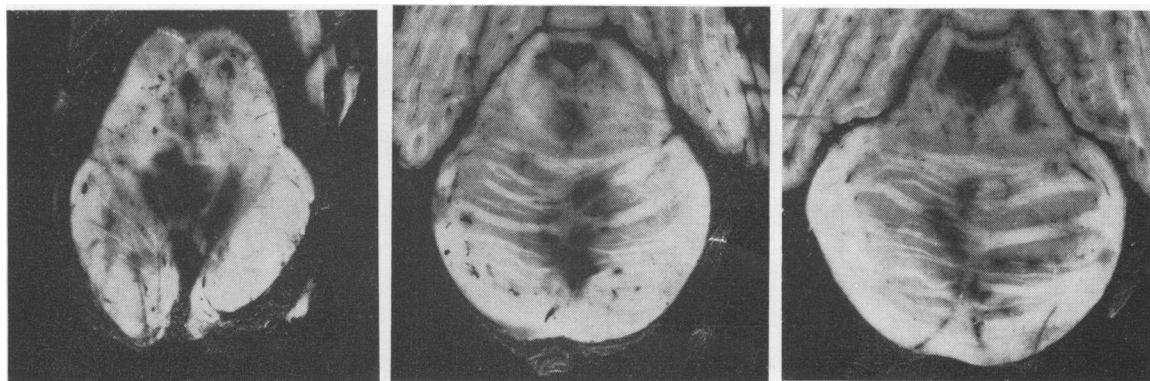


Fig. 3 Typical central pontine and mid-brain haemorrhages found after tentorial herniation from a man of 28 years who died within one and a half hours of a severe head injury. Also present were multiple cortical contusions and massive hemisphere swelling. The rostral mid-brain photograph suggests moderate antero-posterior elongation.

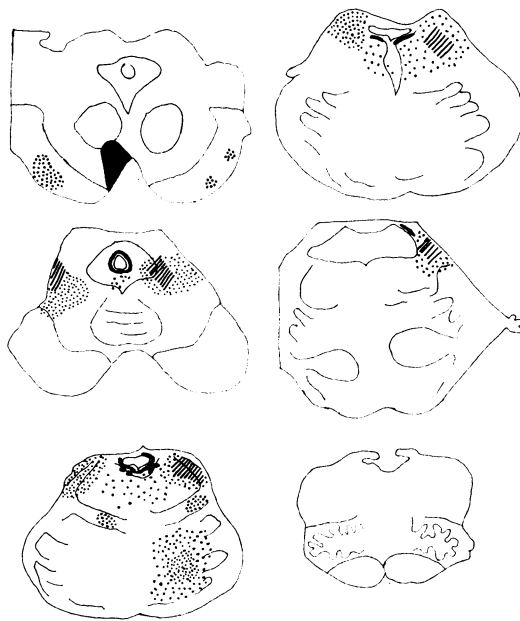


Fig. 4 Diagrammatic representation of brain-stem lesions in a woman of 73 years who died in coma seven days after a head injury. There was no evidence of herniation: the brain was small (1,080 g) with a considerable gap between brain and skull; there was no sub- or extradural bleeding and only small haemorrhages in the cerebrum, particularly in the corpus callosum. The solid black areas represent haemorrhage, the lines foci of ischaemic necrosis, and the stippled areas the sites of axon retraction balls.

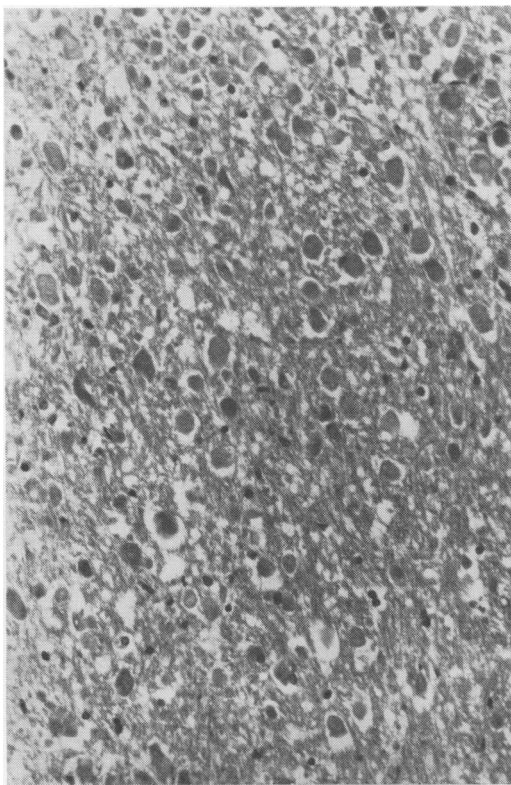


Fig. 5a Numerous axon retraction balls in the upper pons in a woman of 73 years who died in coma seven days after a head injury. Haematoxylin and eosin,  $\times 190$ .

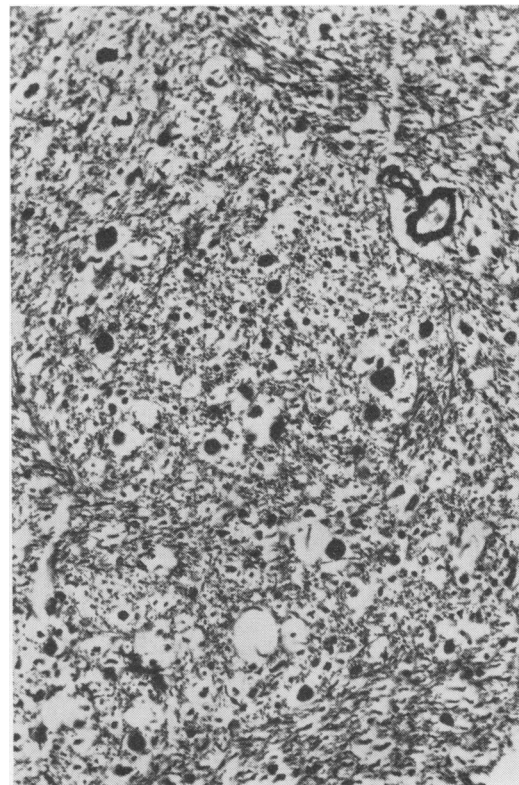


Fig. 5b Middle cerebellar peduncle showing less numerous but more densely stained axon retraction balls in a silver impregnation. From a man of 41 years dying seven days after head injury. Other evidence of tract degeneration also seen. Gleses and Marsland,  $\times 190$ .

### Delayed Changes from Primary Injury

#### DAMAGE TO AXONS

Though some primary haemorrhages may be found in the rostral stem in cases surviving for days or weeks, other primary changes become apparent, particularly in those who had been in coma from the time of the injury and without evidence of tentorial herniation. Damage to nerve fibres is important. This was first described by Strich (1956 and 1961) particularly in the hemispheres. Axon damage can be detected in haematoxylin and eosin sections in most cases; it tends to occur in certain sites, those where primary haemorrhages are often found in rapidly fatal cases, and to involve certain fibre tracts, particularly in the mid and rostral pons and the mid-brain (Fig. 4). In the early days after injury, fibre damage is manifest by the appearance of axon retraction balls (Fig. 5a and b), usually interpreted as axoplasm escaping from the ends of torn axons. In addition, many axons are swollen or grossly distorted. Retraction balls may be few or many in the descending corticospinal and corticopontine fibres of the upper pons, and occasionally are numerous in pontocerebellar fibres. Not infrequently these tracts show large

masses of axon balls in a single section, suggesting that many axons were torn at approximately the same level. In sections a few millimetres above and below, there may be little or no evidence of axon destruction, strongly supporting the localization of injury. Similar evidence of severe axon damage may be found in the superior cerebellar peduncles, with involvement of the neighbouring lateral lemniscus and central tegmental tract, in the medial lemniscus, and in the decussation of the brachium conjunctivum. The tissues adjacent to the lateral mesencephalic sulcus are often most severely involved. Here numerous tracts may be damaged, including the lateral spinothalamic, spinotectal, and the lateral tectopontine tracts, the lateral lemniscus, and the lateral limits of the central tegmental tract. Damage may not be limited to torn axons: it ranges from isolated retraction balls to almost total destruction of all elements, with or without some haemorrhage. Retraction balls may be found more rostrally in the basis pedunculi, in the peduncle of the inferior colliculus, in the colliculus itself, and in the caudal diencephalon. Figure 4 shows the distribution of damaged axons in a patient who died from pneumonia seven days after a head injury. Comparison of the distribu-

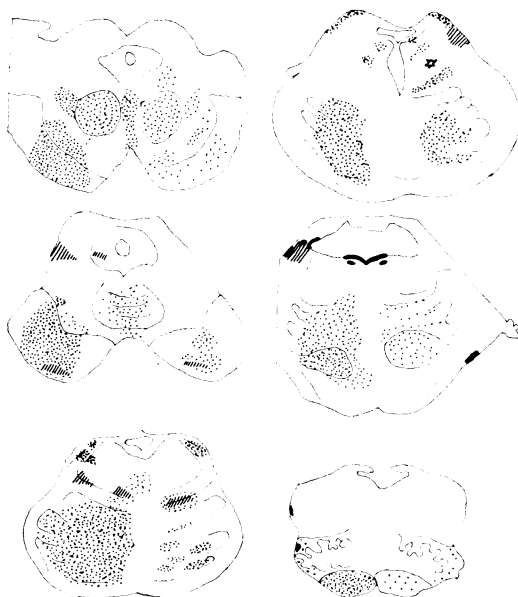


Fig. 6 Diagrammatic representation of brain-stem lesions from a man of 25 years who died four months after a head injury which produced immediate coma from which recovery was insignificant. The stippled areas represent degenerating fibre tracts, the thin lines are areas of ischaemic softening, and the heavy black lines are areas of haemosiderin deposition.

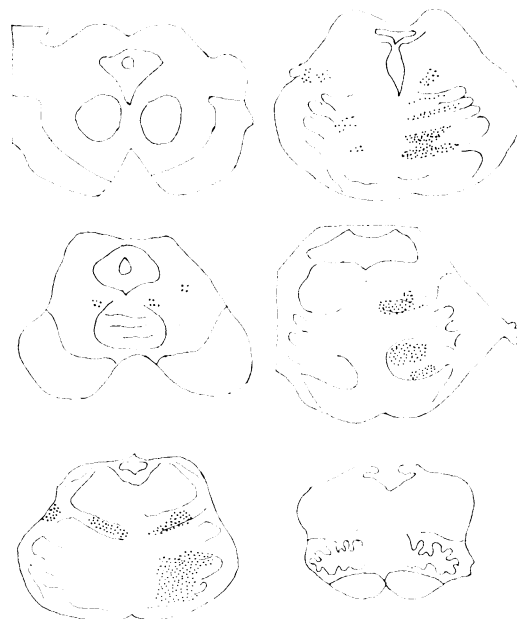


Fig. 7 Diagrammatic representation of the distribution of axon retraction balls in the brain-stem of a woman of 83 years. She was unconscious for four days after a head injury, recovered slowly, and was able to answer simple questions by the fourteenth day when she died from a pulmonary embolism.

tion of the laterally placed lesions in Fig. 4 with those of the laterally placed haemorrhages in the rostral brain stem in Fig. 1 shows a marked similarity. This suggests that similar sites in the upper pons and mid-brain are particularly liable to injury in cases of different severity. Further, the tracts which show retraction balls are virtually the same as those showing Wallerian degeneration in many cases dying after prolonged periods of coma (Fig. 6). Weight is added to this argument by the distribution of retraction balls shown in Figure 7. The sections were from a patient

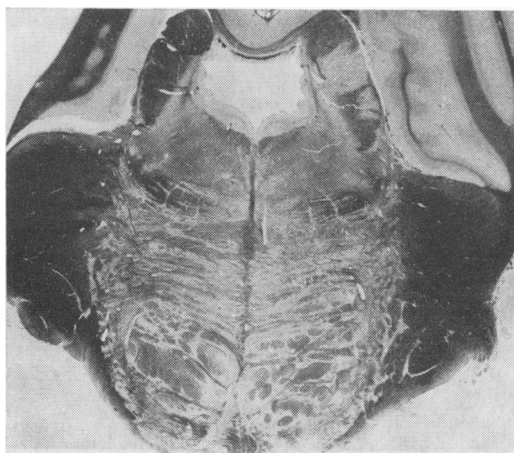


Fig. 8a *Foci of ischaemic necrosis in the right superior cerebellar peduncle from a woman of 73 years surviving in coma seven days after head injury. Neighbouring cerebellar folia also show some ischaemic necrosis. Loyez,  $\times 3$ .*

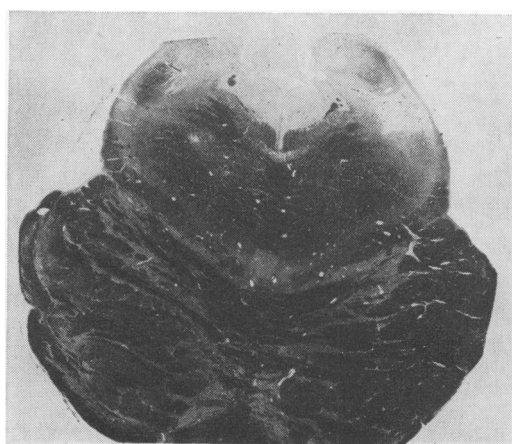


Fig. 8b *Large softening in the right brachium conjunctivum and smaller lesions on the left in a similar position and in the decussation of brachium conjunctivum from a woman of 53 years unconscious for two weeks after head injury and making a considerable recovery. She died from pneumonia nine weeks after injury. Loyez,  $\times 3$ .*

unconscious for four days after a head injury making a slow but progressive recovery and answering simple questions by the 14th day, when death occurred from pulmonary embolism. Many axon balls were present in single sections at the sites indicated though not in the quantity of concentrations found in cases remaining in deep coma.

Of course, not all cases dying in coma of several days' duration show evidence of axon damage in all these sites; brain-stem herniation in some cases produces massive ponto-mid-brain lesions and then it may be impossible to distinguish evidence of primary injury. However, some evidence of axonal damage in the rostral pons, mid-brain, or diencephalon will be found in most cases dying in coma from the time of the accident and without clinical or pathological evidence of herniation. Often it is widespread and severe and involves many of the sites mentioned above.

#### ISCHAEMIC NECROSIS

Destruction of tissue with the appearance of ischaemic necrosis may also be found in the mid-brain in cases dying after the second or third day and in cases which survive many months and even make some degree of recovery. Typical changes of necrosis with macrophage production, gliosis, and cystic change may be seen. Probably the most frequent site for such lesions is again the tissues bordering the lateral mesencephalic sulcus, though the superior cerebellar peduncles, and parts of the colliculi are not infrequently involved (Fig. 8a, b, and c). Lesions may also occur in more central upper pontine and mesencephalic structures and in the diencephalon. These are usually

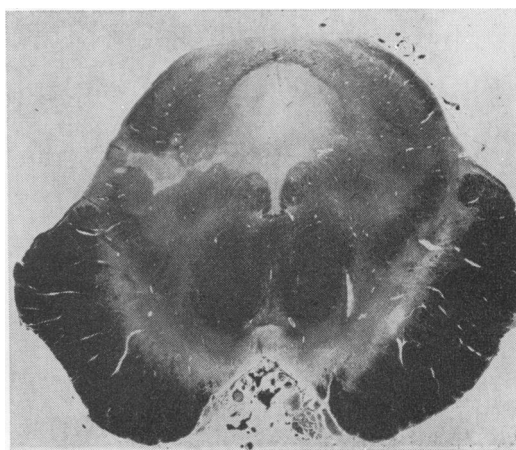


Fig. 8c *Typically placed ischaemic necrosis in the tegmentum adjacent to the left lateral mesencephalic sulcus from a man of 41 years unconscious for seven days after head injury. A similar smaller area of ischaemic necrosis is present in the centre of the right caudal substantia nigra. Loyez,  $\times 3$ .*



microscopic in size but they may be visible to the naked eye. Some haemorrhage may be associated with the infarcts in cases dying during the first 10 days and the surrounding area may be thick with retraction balls, but often no haemorrhages are present. In patients dying after some weeks or months, it may be impossible to demonstrate haemosiderin in the resulting softening. Thrombosed arterioles and venules and fibrinoid necrosis of other small vessels were found in three cases with haemorrhagic infarcts. Serial sections from cases with infarcts have not been examined, but thrombosis of blood vessels damaged by stretching or distortion at the time of injury may be responsible for some of the lesions.

Infarcts, then, though small, are a relatively frequent sequel of severe injury to the mid-brain; many occur at the same sites as primary haemorrhages in cases dying quickly and at similar sites to the concentrations of axon balls in cases dying after several days. The relative constancy of the

sites of small infarcts can be judged by comparing the illustrations in this paper with those of Strich (1961 and 1969), Denny-Brown (1962), Zülch (1966), and Jellinger and Seitelberger (1969). Of course, they may be found in brains with central lesions resulting from herniation, but lateral lesions alone are rarely found in cases of herniation without the more typical central lesions.

#### FOCI OF MICROGLIAL PROLIFERATION

The infarcts show the usual macrophage response, and these cells are loaded with sudanophilic lipid after seven to 10 days. By contrast, cellular response to axon retraction balls is often minimal or apparently absent even when the majority of fibres in a tract are damaged. Nevertheless, foci of microglial proliferation are present in the brains of many cases (Fig. 9). These are often situated around or close to vessels, sometimes in association with small haemorrhages or degenerating axons, but sometimes without other evidence of injury. They vary in size from 100 microns to a millimetre in diameter. They occur both in fatal cases and in patients recovering from relatively minor injuries but dying of other causes (Oppenheimer, 1968). They also occur in the brain-stem, particularly in the tegmentum and brachium conjunctivum and the lateral and ventral surfaces of the pons (Oppenheimer, 1968). Oppenheimer made a special study of microglial foci in the injured brain and illustrates their development from the time of their first appearance at about 15 hours after injury. Although they are distributed like primary lesions they appear to be more widely scattered than the other primary effects.

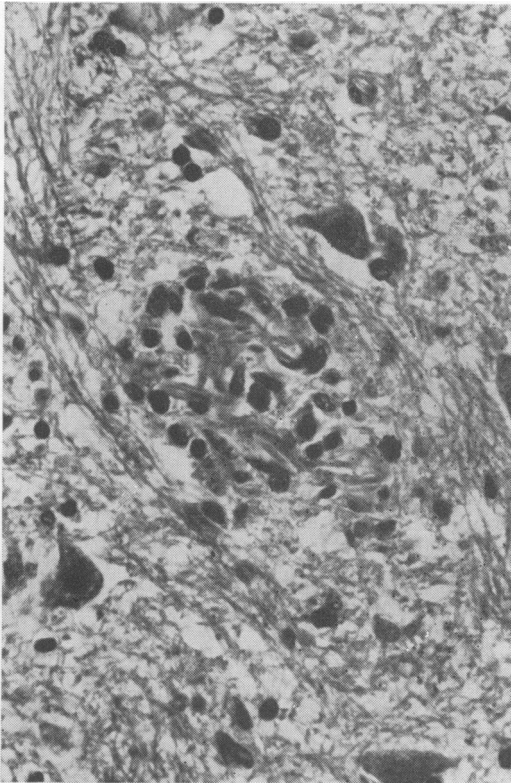


Fig. 9 *Focus of microglial proliferation in the rostral pons from a man of 53 years dying of bronchopneumonia 16 days after an apparently trivial head injury which produced deep unconsciousness for only five minutes though he remained aggressive and confused until shortly before death. Two or three similar foci, some associated with small haemorrhages, were present in each section examined between the mid-pons and inferior colliculus. Haematoxylin and eosin,  $\times 480$ .*

#### LESIONS IN PATIENTS DYING AFTER MONTHS IN COMA

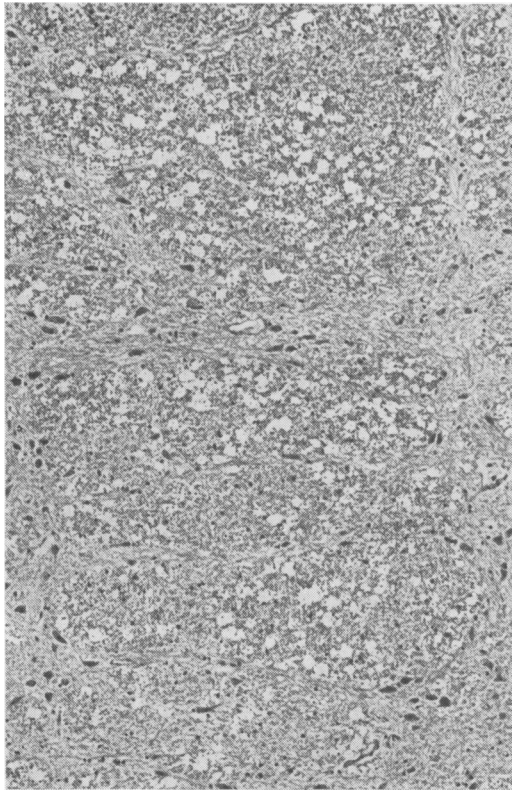
Brain-stem lesions are also found in most subjects who die after having been in coma for weeks or months, and in some who partially recover, but come to necropsy after a long interval. Most of these are related to the lesions already described.

Thus areas of old ischaemic softening in the rostral pons and tegmentum, usually predominantly midline, are found in those who survive tentorial herniation (Wolman, 1953) (Fig. 2). Occasionally they are very extensive and the pons is visibly shrunken from loss of its central tissues (Tomlinson, 1964). Frequently, however, many of the changes found are the result of primary damage to the brain-stem, with, in addition, degeneration of descending fibre tracts from destruction of tissue above the tentorium and retrograde atrophy of neurone masses following interruption of their axons.

Degenerating corticopontine and corticospinal fibres in the peduncles, pons, and medulla are particularly prominent in cases of coma of long duration. With experience, these changes are



readily recognized in paraffin sections stained with haematoxylin and eosin, appearing as markedly vacuolated tracts containing many empty, irregular spaces with rather ragged delicate margins: under high power these are recognizable as macrophages. The tract abnormality is readily recognized by pallor in preparations stained for myelin, in frozen sections stained for neutral fat, and in Marchi preparations (Fig. 10a, b, and c). Pyramidal tract degeneration is often visible to the naked eye in the medulla in cases surviving several months where one pyramid may be greyish brown as a result of demyelination. Both pyramids are usually degenerate, but, as Strich (1956 and 1961) has emphasized, equal bilateral

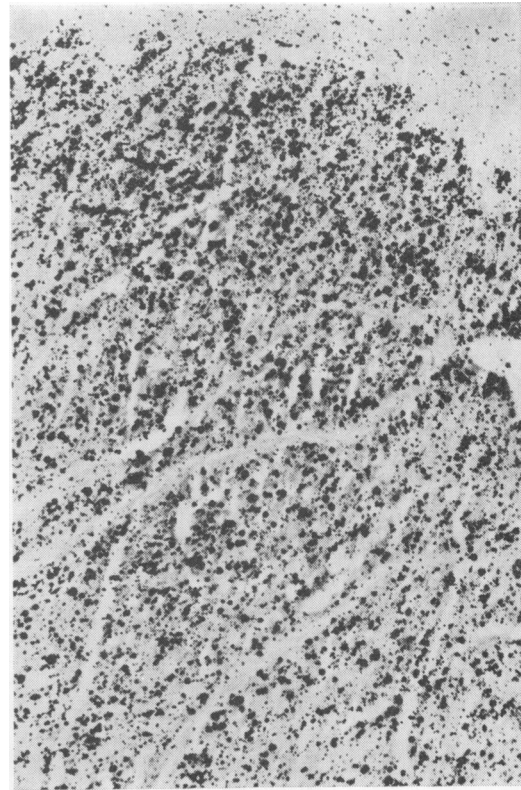


10a

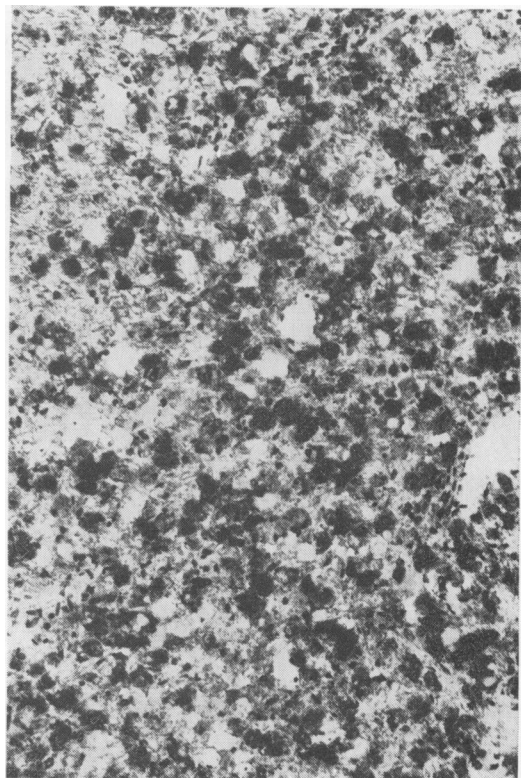
**Fig. 10a** *Degeneration of descending cortical fibres in the pons from a man aged 24 years who survived 15 weeks from the time of injury. He was decerebrate when first seen, deeply unconscious and only showed slight lightening of his conscious state up to the time of death. Haematoxylin and eosin,  $\times 80$ .*

**Fig. 10b** *Degeneration of descending cortical fibres (same case as Fig. 10a). Marchi,  $\times 48$ .*

**Fig. 10c** *Massive degeneration in the brachium conjunctivum, the dark structures being fat-filled macrophages. From the same case as Figure 6. Fat Red 7B,  $\times 120$ .*



10b



10c

involvement of descending tracts is uncommon (Fig. 11). Sometimes the greater part of the descending fibre tract degeneration can be traced from above the tentorium and the internal capsule thereby confirming that hemisphere lesions (Strich, 1956 and 1961) have been largely responsible. In other cases, extensive lower pontine and medullary tract degeneration is not associated with an equivalent rostral degree of degeneration, suggesting, as the studies of cases dying after a few days indicated, that much disruption of fibres often occurs at the level of the brain-stem. Sudanophilic material develops slowly in the degenerating tracts and strongly positive staining with Sudan IV, Scharlach R, or Fat Red 7B takes months to develop (Fig. 10c). Much material is in the form of birefringent crystals, well seen in unstained frozen sections; and Marchi preparations may be strongly positive after several weeks. Cellular response, apart from macrophages, is relatively slight, consisting of occasional prominent astrocytes in and around the degenerating tracts, and occasional glial clusters, though these may be found in areas not involved by tract degeneration. The tracts most affected are those in which retraction balls are seen in large numbers in cases dying earlier. Thus cortico-spinal and cortico-pontine tracts, ponto-cerebellar fibres, medial lemniscus, brachium conjunctivum, lateral and medial tegmental tracts are commonly involved. Superior and middle cerebellar peduncles may show scattered or large clusters of degenerating fibres. In addition, small cystic foci of softening up to 5 mm across may be present, particularly in the superior cerebellar peduncles, the lateral margins of the inferior collicular brachium, and the tissues

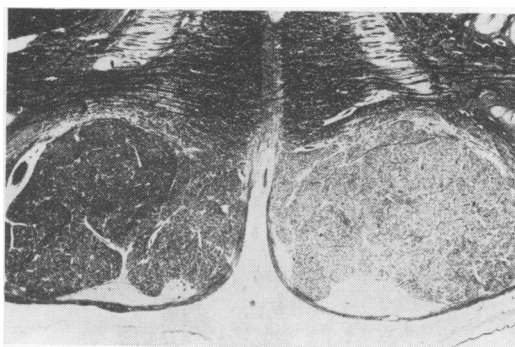


Fig. 11 Gross demyelination of one pyramid and partial demyelination of the other from a man of 33 years dying 14 months after a head injury. He was unconscious for several weeks and made only a very partial recovery, being aphasic, hemiplegic, and totally apathetic until his death from pneumonia. Numerous other brain-stem tracts showed severe degeneration but there was marked degeneration of hemispherical white matter so that the pyramidal degeneration may have resulted from hemisphere damage. Loyez,  $\times 12$ .

adjacent to the lateral mesencephalic sulcus. Occasionally other minute softenings, 100  $\mu$  to 500  $\mu$  diameter, with or without iron-pigmented macrophages, may be present elsewhere, and indeed almost anywhere in the upper pons, mid-brain tegmentum, the tectum, peduncles, substantia nigra, or posterior hypothalamus. Periventricular and peri-aqueductal tissues are probably where these small remnants of the original disrupted foci are most often found.

In addition, a more diffuse though usually light gliosis, and scattered macrophages may be present, particularly in the mid-brain. In many cases, marked shrinkage of the whole brain-stem occurs, easily recognizable to the naked eye, even in the uncut specimen; the pons may present slight bilateral concavities on its ventral surface mainly from loss of fibre bulk. Different cases present with particular changes, such as traumatic lesions of various cranial nerves with marked chromatolysis of the corresponding neurones. An impression of widespread neuronal loss in the pons and mid-brain is often gained from sections in cases of prolonged unconsciousness, but an objective assessment would require an exhaustive and carefully controlled neuroanatomical study, which so far has not been attempted.

#### Brain-stem Lesions after Head Injury in Patients Dying of Extracerebral Causes

Those who become conscious after many weeks and survive for months or years with varying degrees of physical and mental impairment often show changes similar to those found in cases dying after prolonged continued coma. The lesions shown diagrammatically in Fig. 6, from a man in coma from injury to death, are very similar in distribution and type to those found in a case in which recovery from coma took almost three months. The latter patient eventually returned home for several months, remained aphasic and hemiplegic (possibly from hemisphere lesions), apathetic, and almost completely helpless, though apparently aware of his surroundings. Figure 8b is from a woman who began to recover consciousness two weeks after injury; after nine weeks, when she developed a rapidly fatal pneumonia, she was feeding herself, walking a little with the aid of a stick, and talking sensibly for short periods. In addition to the characteristically placed mid-brain softenings illustrated, severe third nerve degeneration was present.

The frequency of these changes and their severity in patients recovering from mild head injury with short periods of unconsciousness is not known. Oppenheimer (1968) recorded myelin destruction, axon retraction balls, and microglial clusters in the brain-stem of patients who had suffered relatively trivial concussion. In one

personally studied case many widely scattered retraction balls were present in cortico-spinal and cortico-pontine fibres; that patient also had a serious chest injury and died five days after the accident. In another patient who had been unconscious for five minutes and died 16 days later from bronchopneumonia, a few retraction balls were present ventral to one inferior colliculus, occasional small perivenous haemorrhages were found in the ventral and lateral tissues of the upper pons, and microglial foci (Fig. 9) were observed in the rostral pons and caudal mid-brain. These are very similar to the lesions illustrated by Oppenheimer (1968) who suggested that they possibly resulted from displaced vessels damaging neural tissue.

Evidence is therefore accumulating that brain-stem lesions occur not only in the great majority, if not all cases of severe head injury with prolonged unconsciousness, but also in at least some cases of minor head injury associated with temporary unconsciousness. In both, the brain-stem damage is similar in distribution and type though the severity varies.

### Conclusions and Summary

Severe injuries produce tearing of various blood vessels and bleeding in certain sites of the brain-stem. When bleeding is widespread, death is extremely rapid and there is no time for severe haemorrhagic disruption of the stem to occur. In such cases it must be assumed that damage to neural tissue is also severe and widespread; the lesions would be demonstrable with longer survival, or if histological techniques capable of showing immediate neural damage were available. Neural damage produced at the time of injury becomes manifest when injury to the stem is not so widespread or severe and the patient survives for many hours or several days. Haemorrhages may be present but they are usually confined to the rostral brain-stem; they have a distribution similar to those found in rapidly fatal cases, unless herniation of the brain-stem has also occurred. Infarcts develop in many cases without evidence of herniation and these are largely sited in the rostral stem where primary haemorrhages are conspicuous. Therefore these infarcts probably result from damage to small blood vessels of a severity less than that which produces tearing and haemorrhage. Thrombosis or necrosis of small vessels near the infarcts is sometimes demonstrable. Examination of serial sections may show that such injuries to small blood vessels are frequent and the cause of the infarcts. Damaged axons are demonstrable in many cases surviving for several days. They occur in similar sites to the primary haemorrhages and infarcts and also in certain more centrally placed fibre tracts. The sites of the retraction balls seen

in cases dying several days after injury coincide with the common sites of primary haemorrhage in the rostral stem, with the fibre-tract degeneration found in many cases surviving in coma for weeks or months, and also in some who partially recover. Axon damage of lesser severity but in similar locations has been demonstrated in some cases with relatively minor head injury. All the above features point to a common direct result of the primary injury.

Primary damage to structures rostral to the mid-brain may also lead to fibre-tract degeneration, and secondary herniation at the tentorial hiatus may produce further haemorrhagic or ischaemic lesions. The latter are predominantly central in situation. Jellinger and Seitelberger (1969) attribute all brain-stem necrosis and haemorrhage in long-surviving cases to tentorial herniation and suggest that the more lateral location of many lesions 'must result from factors somewhat different from those operative in acute fatal cases', when the lesions are more centrally placed. It is possible that laterally placed lesions of primary distribution can occur from herniation without central lesions, but they must be uncommon except for peduncle damage from lateral movement of the stem. The evidence, contrary to this view of Jellinger and Seitelberger and gathered from cases dying at different intervals after injury and from patients without evidence of herniation, is strong.

Quite apart from the frequency and variety of primary brain-stem lesions presented in this paper and by other authors (Strich, 1956, 1961, and 1969; Crompton, Teare and Bowen, 1966a and b; Oppenheimer, 1968), the possibility that primary brain-stem damage in man is associated with temporary unconsciousness is attractive in that it forms a possible link with the lesions found after experimental concussion in animals.

Early observations recorded chromatolysis and some loss of brain-stem neurones in different animals after concussive blows (Windle, Groat, and Fox, 1944; Groat, Windle, and Magoun, 1945; Windle, Rambach, Arellano, Groat, and Becker, 1946). After repeated, spaced, concussive blows to guinea-pigs, Windle and Groat (1945) showed that up to half the large interneurons of the reticular formation in the brain-stem and cells of the lateral vestibular nucleus could be lost. Similar changes have not been described in man after trivial or even severe head injury nor, to my knowledge, is the quantitative information of the nerve cell population of the brain-stem in man sufficient to allow such work to be attempted. Even if it were, the opportunities of examining the brain in cases of simple concussion are excessively rare. Evidence of myelin degeneration in the guinea-pig brain-stem (Windle, 1948) and damage to nerve fibres with consequent Wallerian degeneration in cats (Friede, 1961) have, however, also been described after experimental concussion and also occasional

local cellular proliferation (Bryan and Walker, 1969). These experimental findings are not dissimilar in character to those seen in some cases of head injury with short periods of unconsciousness. Variations in detail, particularly in relation to the site of the lesions in man and experimental animals, is to be expected if only because of the neuroanatomical differences. Further work may yet prove that the morphological changes in animals concussed experimentally and in man after accidental concussion are essentially similar.

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